National Phase of Int'l Amin. No. PCT/US00/26797

A method of treating a host infected with a virus of the Flaviviridae, 35. (New) Rhaboviridae or Paramyxoviridae family, which method comprises administering to the host an inhibitor of dihydroorotate dehydrogenase.

A method according to claim 35, wherein the inhibitor is a compound 36. (New) of the formula (I):

$$A = \underbrace{\frac{a}{\|}}_{N} (A)_{n}$$

$$R$$
(I)

wherein:

Inclusion each A is independently selected from the group consisting of hydrogen, halogen, perhaloalkoxy, amino C₁-C₈ alkyl, NO₂, CN, SO₂CH₃, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, aryl, aryloxy, C₁-C₆ perhaloalkyl and Y, or two adjacent groups A on ring b form, together with the phenyl ring to which they are attached, a naphthalene ring system;

R is cyclohexyl, phenoxy or benzoxy, or a phenyl ring which is unsubstituted or substituted by a group A as defined above; or

R and an adjacent group A on ring b form, together with the phenyl ring to which they are attached, a naphthalene or phenanthrene ring system;

Y is selected from the group consisting of COOM, CONHR', SO₃M and hydrogen M is selected from the group consisting of H, Li, Na, K and O.5 Ca;

National Phase of Int'l April. No. PCT/US00/26797

R' is C_1 - C_{10} alkyl;

n is 1 or 2; and

T is =N- or =C(Z)- wherein either:

- (i) Z is selected from the group consisting of hydrogen, NH₂, OH, C₁-C₈ alkyl, C3-C7 cycloalkyl, aryl and C1-C6 perhaloalkyl, or
- (ii) Z is a bridging moiety selected from the group consisting of -V-W-(wherein V is CH2 or S and W is CH2, O, S or NH) and -(CH2)2 -C(=Z)- wherein Z is O or H₂, the said bridging moiety being attached to the ortho position of ring b of the adjacent biphenyl group, thereby completing a ring.
- A method according to claim 36, wherein the inhibitor is a compound of formula (Ia):

$$A = \underbrace{\frac{a}{N}}_{N} A \qquad (Ia)$$

wherein:

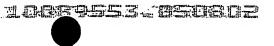
each A is independently selected from the group consisting of hydrogen, halogen, amino C₁.C₈ alkyl, NO₂, CN, SO₂CH₃, C₁-C₈ alkyl, C₃-C₇ cycloalkyl, aryl, C₁-C₆ perhaloalkyl and Y;

Y is selected from the group consisting of COOM, CONHR' SO₃M and hydrogen; M is selected from the group consisting of H, Li, Na, K and O.5 Ca;

R' is C₁-C₁₀ alkyl; and

T is =N- or =C(Z)- wherein either:





- (i) Z is selected from the group consisting of hydrogen, NH₂, OH, C_1 - C_8 alkyl, C_3 - C_7 cycloalkyl, aryl and C_1 - C_6 perhaloalkyl, or
- (ii) Z is a bridging moiety selected from the group consisting of -V-W-(wherein V is CH_2 or S and W is CH_2 , O, S or NH) and -(CH_2)₂ -C(=Z)- wherein Z is O or H_2 , the said bridging moiety being attached to the ortho position of ring \underline{b} of the adjacent biphenyl group, thereby completing a ring.

38. (New) A method according to claim 35, wherein the inhibitor is a compound of the formula (II):

$$\begin{array}{c|c}
COOM \\
R^{1} \\
\underline{a} \\
N
\end{array}$$

$$\begin{array}{c|c}
R^{3} \\
\underline{b} \\
R^{5}
\end{array}$$
(II)

wherein

R¹ is H, a halogen or OCF₃;

 R^2 is H or C_1 - C_6 alkyl;

 R^3 is H or OR^6 wherein R^6 is H or C_1 - C_6 alkyl;

 R^4 is H or C_1 - C_6 alkyl; or R^4 and R^3 form, together with phenyl ring \underline{b} to which they are attached, a naphthalene ring; and

 R^5 is cyclohexyl, phenyl or benzoxy, or a phenyl ring which is unsubstituted or substituted by halogen; or R^4 and R^5 form, together with phenyl ring \underline{b} to which they are attached, a phenanthrene ring.

39. (New) A method according to claim 38, wherein the inhibitor is a compound of formula (IIb):

National Phase of Int'l Amln. No. PCT/US00/26797

wherein M is H or Na.

A method according to claim 35, wherein the inhibitor is a compound of 40. (New) formula (I'):

$$A \xrightarrow{Y} R'$$

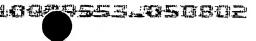
$$R''$$

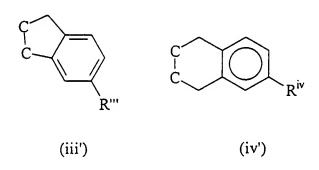
$$R''$$

wherein A and Y are as defined above for formula (I);

R' is hydrogen and R'' is a thiophene ring or a group of formula (i') or (ii'):

or R' and R" form, together with the carbon atoms (denoted "C") to which they are attached, a ring system of formula (iii') or (iv'):







wherein R''' is H or halogen and R^{iv} is H or C_1 - C_6 alkoxy.

41. (New) A method according to claim 35, wherein the inhibitor is a compound of the formula (III):

$$A^{1} \underbrace{\underline{a}}_{O} \underbrace{\underline{b}}_{A^{1}}$$
 (III)

wherein:

each A¹ is independently selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₇ cycloalkyl, halogen, unsubstituted aryl, X-substituted aryl, NO₂, CN, COOR, CONHR and NHR; X is selected from the group consisting of halogen, NO₂, C₁-C₈ alkyl, aryl, fused aryl and COOR;

R is selected from the group consisting of hydrogen and C_1 - C_8 alkyl; and B is selected from the group consisting of C_1 - C_8 alkyl, H, CF₃ and aryl which is unsubstituted or substituted by halogen, C_1 - C_8 alkoxy, C_1 - C_8 alkyl, NO₂, aryl or fused

National Phase of Int'l A

n. No. PCT/US00/26797

aryl.

42. (New) A method to claim 41, wherein the inhibitor is a compound having the formula (IV):

43. (New) A method according to claim 35, wherein the inhibitor is a compound having the formula (V):

$$A^{2} \xrightarrow{CX^{1}_{2}CX^{1}} = C$$

$$Z^{1}$$

$$(V)$$

wherein:

 A^2 is selected from the group consisting of hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_7 cycloalkyl, halogen, unsubstituted aryl, halogen-substituted aryl, fused aryl, NO_2 , CN, NHR^1 and $N(R^1)_2$;

R¹ is selected from the group consisting of hydrogen, C₁-C₈ alkyl and OH;

X¹ is hydrogen or halogen; and

B1, Y1 and Z1 are each independently selected from hydrogen,

OH, C₁-C₈ alkyl, halogen, CN, NO₂ and CF₃.

44. (New) A method according to claim 35, wherein the inhibitor is a compound having the formula (VI):

$$\begin{array}{c}
O \\
CH_2CH = C \\
CI \\
OH
\end{array}$$
(VI)



A method according to claim 35, wherein the inhibitor is a compound having the formula (VII):

$$A^3$$
 B^2
 A^3
 A^3

wherein:

each A3 is independently selected from the group consisting of hydrogen, C1-C8 alkyl, C₁-C₁₀ alkoxy, halogen and N(R²),;

B² is a direct bond, -CH=CH- or -C≡C-:

X² is selected from the group consisting of O, S and NR²;

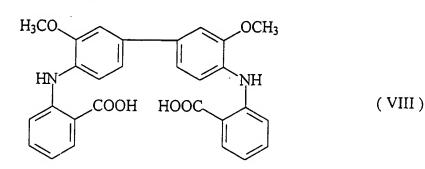
 R^2 is selected from the group consisting of hydrogen, C_1 - C_4 alkyl and aryl;

 Y^2 is selected from the group consisting of COOM¹ and SO_3M^1 ; and

M1 is selected from the group consisting of H, Li, Ha, K and 0.5 Ca.

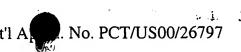
A method according to claim 45, wherein the inhibitor is a compound 46. (New) having the formula (VIII):

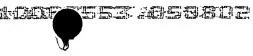






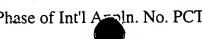
- 47. (new) A method according to claim 35, wherein the virus is a flavivirus selected from the group consisting of hepatitis viruses, yellow fever virus, West Nile virus, kunjin virus, dengue virus, St. Louis encephalitis virus, Japanese encephalitis virus, Murray valley encephalitis virus and tick-borne encephalitis virus.
- 48. (New) A method according to claim 47, wherein the virus is a rhabdovirus selected from vesicular stomatitis virus and rabies virus, or is the paramyxovirus RSV.
- 49. (New) A method according to claim 35, wherein the medicament is for administration with an interferon.
- 50. (New) A method according to claim 35, wherein the medicament further comprises an interferon.
- 51. (New) A method according to claim 49, wherein the interferon is a human interferon.
- 52. (New) A method according to claim 50, wherein the interferon is human interferon.
- 53. (New) A method according to claim 49, wherein ther interferon is selected from the group consisting of interferon $\alpha 2$, interferon $\alpha 8$ and interferon β .
- 54. (New) A method according to claim 50, wherein the interferon is selected from the group consisting of interferon $\alpha 2$, interferon $\alpha 8$ and interferon β .
- 55. (New) A method according to claim 49, wherein the interferon is human interferon α8 having a specific activity of from 0.3x109 to 3x109 IU per mg protein.





- 56. (New) A method according to claim 50, wherein the interferon is human interferon α8 having a specific activity of from 0.3x10° to 3x10° IU per mg protein.
- 57. (New) A method according to claim 49, wherein the interferon is human interferon β having a specific activity of from $2x10^8$ to $8x10^8$ per mg protein.
- 58. (New) A method according to claim 50, wherein the interferon is human interferon β having a specific activity of from 2x108 to 8x108 per mg protein.
- 59. (New) A method according to claim 49, wherein the inhibitor and the interferon are used in respective amounts which produce a synergistic effect.
- 60. (New) A method according to claim 50, wherein the inhibitor and the interferon are used in respective amounts which produce a synergistic effect.
- 61. (New) A method according to claim 35, wherein the medicament is for use with an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase.
- 62. (New) A method according to claim 61, wherein the medicament further comprises the inhibitor of the said second enzyme.
- 63. (New) A method according to claim 61, wherein the inhibitor is mycophenolic acid, cyclopentenyl cytosine (CPE-C) or 3-deazaneplanocin A.
- 64. (New) A method according to claim 62, wherein the inhibitor is mycophenolic acid, cyclopentenyl cytosine (CPE-C) or 3-deazaneplanocin A.
- 65. (New) A method according to claim 61, wherein the inhibitor of the second enzyme and the inhibitor of dihydrooratate dehydrogenase are used in respective amounts which produce a synergistic effect.
- 66. (New) A method according to claim 62, wherein the inhibitor of the second enzyme and the inhibitor of dihydrooratate dehydrogenase are used in respective amounts which produce a synergistic effect.
- 67. (New) A method according to claim 63, wherein the inhibitor of the second enzyme and the inhibitor of dihydrooratate dehydrogenase are used in respective amounts which produce a synergistic effect.
 - 68. (New) A compound of formula (IIa):





$$R^{22}$$
 R^{33}
 R^{44}
 R^{55}
(IIa)

wherein

M is selected from the group consisting of H, Li, Na, K and 0.5 Ca;

 R^{22} is H or C_1 - C_6 alkyl;

R³³ is H or OR⁶ wherein R⁶ is H or C₁-C₆ alkyl;

R⁴⁴ is H or C₁-C₆ alkyl; and

R⁵⁵ is phenyl, cyclohexyl, phenoxy or benzoxy;

or a metabolite or prodrug precursor thereof.

- 69. (New) A compound according to claim 68, which is selected from:
- 2-(4-biphenylyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K5);
- 2-(4-biphenylyl)-3-methyl-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K55);
- 2-(4-cyclohexylphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K46);
- 2-(4-benzyloxy-2-methoxy-3-methyl-phenyl)-6-trifluoromethoxy-quinoline-4carboxylic acid (compound I2K51); and
- 2-(4-phenoxyphenyl)-6-trifluoromethoxy-quinoline-4-carboxylic acid (compound I2K52).
- A process for producing a compound of formula (IIa) as claimed in 70. (New) claim 68, which process comprises
- a) condensing a trifluoromethoxy-substituted isatin compound of the following formula (IX):

with a ketone of formula (X):

$$R^{22}CH_2$$
 R^{33}
 R^{44}
 R^{55}
 R^{55}

wherein R^{22} , R^{33} , R^{44} and R^{55} are as defined in claim 60, in the presence of a base; and

- (b) if desired, converting a resulting compound of formula (IIa) in which M is H into a pharmaceutically acceptable sait thereof wherein M is Li, Na. K or 0.5 Ca.
- 71. (New) An anti-flavivirus, anti-rhabdovirus or anti-paramyxovirus agent comprising an inhibitor of dihydroorotate dehydrogenase.
- 72. (New) Products containing an inhibitor of dihydroorotate dehydrogenase and an interferon as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.
- 73. (New) Products containing an inhibitor of dihydroorotate dehydrogenase and an inhibitor of a second enzyme selected from inosine monophosphate dehydrogenase, guanosine monophosphate synthetase, cytidine triphosphate synthetase and S-adenosylhomocysteine hydrolase as a combined preparation for simultaneous, separate or sequential use in treating an infection attributable to a virus of the Flaviviridae, Rhabdoviridae or Paramyxoviridae family.
- 74. (New) Products according to claim 73, which additionally contain an interferon.

